

BIOLOGICALLY ABSORBABLE COATINGS FOR IMPLANTABLE DEVICES BASED
ON COPOLYMERS HAVING ESTER BONDS AND METHODS FOR FABRICATING
THE SAME

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BACKGROUND

1. Field of the Invention

This invention is directed to coatings for drug delivery devices, such as drug eluting vascular stents, and methods for producing the same.

10 2. Description of the State of the Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned
15 across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress against the atherosclerotic plaque of the lesion to remodel the lumen wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or
20 torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the

procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, a stent is implanted in the lumen to maintain the vascular patency.

5 Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired
10 location. Examples in patent literature disclosing stents which have been applied in PTCA procedures include stents illustrated in U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No. 4,886,062 issued to Wiktor.

 Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide
15 an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. One proposed method for medicating
20 stents involves the use of a polymeric carrier coated onto the surface of a stent. A solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The solvent is allowed to evaporate, leaving on

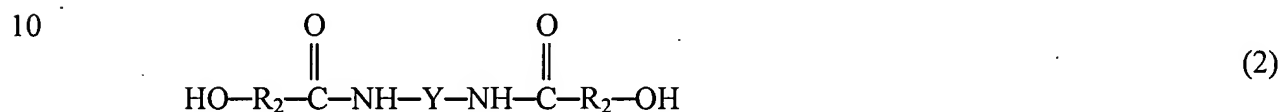
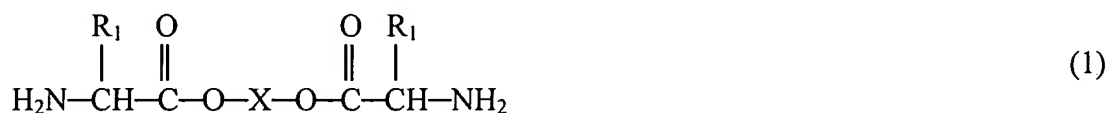
the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

One polymer that can be used for making stent coatings for local drug delivery can be selected from a group of poly(ester amides) described in U.S. Patent No. 6,503,538 to Chu et al. However, some mechanical properties, such as hardness of the poly(ester amides) taught by Chu et al. may be insufficiently good for stent applications. Accordingly, there is a need to have poly(ester amides) with better properties to allow the poly(ester amides) to be used to make stent coatings for local drug delivery.

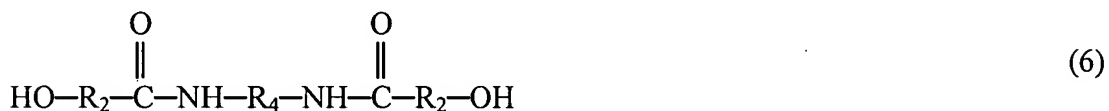
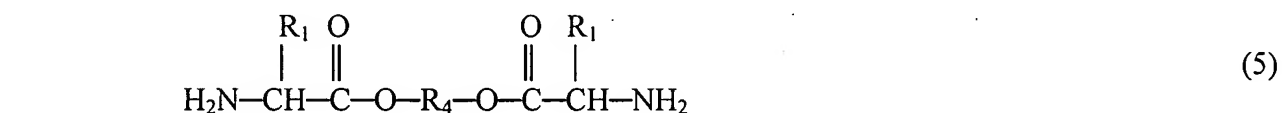
SUMMARY

According to one aspect of the present invention, a medical article is provided, the article comprises an implantable substrate having a coating, the coating includes a polymeric product of a reaction between a first reagent, a second reagent, and a third reagent, wherein

5 the first reagent can be one of the compounds having formulae (1), (2), (3), and (4):



the second reagent can be one of the compounds having formulae (5), (6), (7), and (8):



(c) the third reagent can be a dicarboxylic acid having the formula (9):



In formulae (1)-(9), R₁ can be hydrogen, methyl, *iso*-propyl, *sec*-butyl; *iso*-butyl, or benzyl group; R₂ can be methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylenemethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group; R₃ can be a straight chained or branched aliphatic alkylene group C_nH_{2n}, wherein n is an integer between 2 and 12; R₄ can be a moiety derived from a compound selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic acid, poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone, and cellulose; X can be a straight chained or branched aliphatic alkylene group C_nH_{2n}, wherein n is an integer between 2 and 12; and Y can be a straight chained or branched aliphatic alkylene group C_nH_{2n}, wherein n is 1, 2, or 5.

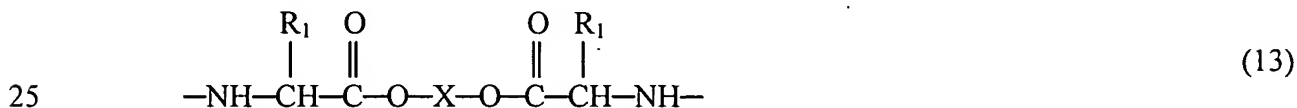
According to another aspect of the present invention, a medical article is provided, the article comprises an implantable substrate having a coating, the coating includes a copolymer having a general formula (10) or (11):



wherein M can be a moiety represented by the structure having the formula (12)

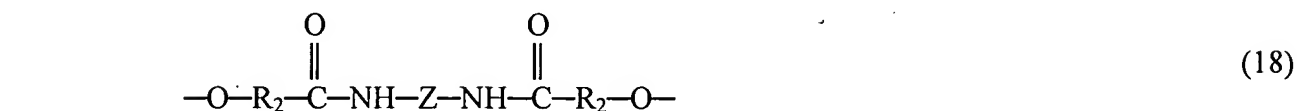
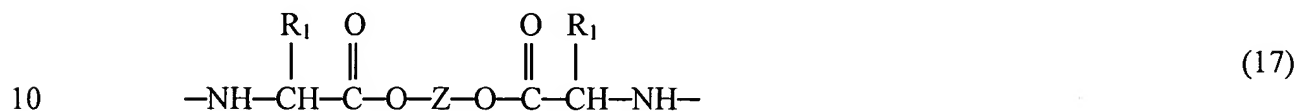


P can be one of the moieties having the formulae (13), (14), (15), and (16):





Q can be one of the moieties having the formulae (17), (18), and (19)



and M₁ can be a moiety represented by the formula (20):



In formulae (10)-(20), R₁ can be hydrogen, methyl, *iso*-propyl, *sec*-butyl; *iso*-butyl, or benzyl group; R₂ can be methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylenemethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group; R₃ can be a straight chained or branched aliphatic alkylene group C_nH_{2n}, wherein n is an integer between 2 and 12; X can be a straight chained or branched aliphatic alkylene group C_nH_{2n}, wherein n is an integer between 2 and 12; Y can be a straight chained or branched aliphatic alkylene group C_nH_{2n}, wherein n is 1, 2, or 5; Z can be a moiety derived from a compound selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic

acid, poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone, and cellulose; and m, n, and p can be integers where the value of m is between 5 and 1,800, the value of n is between 1 and 800 and the value of p is between 4 and 1,500.

5 According to yet another aspect of the current invention, a method for fabricating a medical article is provided, the method includes synthesizing a copolymer and forming a coating based on the copolymer on at least a portion of an implantable substrate, the synthesizing of the copolymer including reacting a first reagent with a second reagent and with a third reagent, wherein the first reagent can be one of the compounds having formulae
10 (1), (2), (3), and (4), the second reagent can be one of the compounds having formulae (5), (6), (7), and (8), and the third reagent is a dicarboxylic acid having the formula (9), where the formulae (1)-(9) are provided above.

 According to yet another aspect of the current invention, a method for fabricating a medical article is provided, the method including synthesizing a copolymer and forming a
15 coating based on the copolymer on at least a portion of an implantable substrate, wherein the copolymer has a general formula (10) or (11), where the formulae (10) and (11) are provided above.

DETAILED DESCRIPTION

1. Terms and Definitions.

The following definitions apply:

The term “biologically absorbable” coatings and/or polymers is defined as coatings and/or polymers that are capable of being completely degraded and/or eroded when exposed to bodily fluids such as blood and are gradually resorbed, absorbed and/or eliminated by the body. The processes of breaking down and eventual absorption and elimination of the coating and/or polymer can be caused, for example, by hydrolysis, metabolic processes, bulk or surface erosion, and the like.

Whenever the reference is made to “biologically absorbable” stent coatings and/or polymers forming such stent coatings, it is understood that after the process of degradation, erosion, absorption, and/or resorption has been completed, no coating, in excess of possibly insignificant trace amount, will remain on the stent. In other words, stent coatings and/or polymers forming such stent coatings are considered “biologically absorbable” if the coatings and/or polymers are substantially broken down by the *in vivo* environment, or by the *in vitro* environment, such as one having physical, chemical, and/or biological characteristics substantially similar to those of the *in vivo* environment. An amount of time needed to break down the coatings and/or polymers can be between about 1 day and several years, or between about 1 day and about 24 months; alternatively, between about 2 months and about 18 months; alternatively, between about 3 month and about 12 months.

For purposes of the present invention, “substantially broken down” means that a substantial reduction of the molecular weight of a polymer occurs as a result of the exposure

of the polymer to the *in vivo* environment or to a simulated *in vivo* environment. The simulated *in vivo* environment can be the *in vitro* environment having physical, chemical, and/or biological characteristics that are identical or substantially similar to those of the *in vivo* environment. Standard analytical techniques normally used by those having ordinary skill in the art can be used to monitor the change of the molecular weight of the polymer. One analytical technique that can be used includes immersing the polymer in a simulated *in vivo* environment and measuring the loss of the molecular weight of the polymer over time. A number of methods can be used for measuring the molecular weight, for example, gel permeation chromatography (GPC). In some embodiments, if the polymer has lost more than about 10 % of its original molecular weight over a 3-month period, then it can be classified as biodegradable.

The term “poly(ester amide)” or “PEA” is defined as a polymer having both at least one ester bond (I) and at least one amide bond (II):



2. Embodiments of the Invention.

A coating for an implantable medical device, such as a stent, according to embodiments of the present invention, can be a multi-layer structure that can include the following three layers:

(a) a drug-polymer layer (also referred to as “reservoir” or “reservoir layer”), comprising a polymer and a drug, or alternatively a polymer free drug layer;

(b) an optional primer layer; and/or

(c) an optional topcoat layer.

5 Each layer of the stent coating can be formed on the stent by dissolving a polymer or a blend of polymers in a solvent, or a mixture of solvents, and applying the resulting polymer solution on the stent by spraying or immersing the stent in the solution. After the solution has been applied onto the stent, the coating is dried by allowing the solvent to evaporate. The process of drying can be accelerated if the drying is conducted at an elevated temperature.

10 To incorporate a drug into the reservoir layer, the drug can be combined with the polymer solution that is applied onto the stent as described above. Alternatively, to fabricate a polymer-free drug layer, the drug can be dissolved in a suitable solvent or mixture of solvents, and the resulting drug solution can be applied on the stent by spraying or immersing the stent in the drug solution.

15 Instead of introducing the drug as a solution, the drug can be introduced as a colloid system, such as a suspension in an appropriate solvent phase. To make the suspension, the drug can be dispersed in the solvent phase using conventional techniques used in colloid chemistry. Depending on a variety of factors, e.g., the nature of the drug, those having ordinary skill in the art can select the solvent to form the solvent phase of the suspension, as
20 well as the quantity of the drug to be dispersed in the solvent phase. The suspension can be mixed with a polymer solution and the mixture can be applied on the stent as described above.

Alternatively, the drug suspension can be applied on the stent without being mixed with the polymer solution.

The drug-polymer layer can be applied directly onto at least a part of the stent surface to serve as a reservoir for at least one active agent or a drug which is incorporated into the reservoir layer. The optional primer layer can be applied between the stent and the reservoir to improve the adhesion of the drug-polymer layer to the stent. The optional topcoat layer can be applied over at least a portion of the reservoir layer and to serve as a rate limiting membrane which helps to control the rate of release of the drug. The topcoat layer can be essentially free from any active agents or drugs.

In one embodiment, any or all of the layers of the stent coating, can be made of a polymer that is both biologically beneficial and biologically degradable, erodable, absorbable, and/or resorbable. In another embodiment, just the outermost layer of the coating can be limited to such a polymer.

To illustrate in more detail, in the stent coating having all three layers described above (i.e., the primer, the reservoir layer, and the topcoat layer), the outermost layer is the topcoat layer, which is made of a biologically absorbable block copolymer. In this case, optionally, the remaining layers (i.e., the primer and the reservoir layer) can be also fabricated of a biologically absorbable block copolymer ; the block copolymer can be the same or different in each layer. If the topcoat layer is not used, the stent coating can have only two layers, the optional primer and the reservoir. The reservoir in this case is the outermost layer of the stent coating and is made of a biologically absorbable block copolymer. Optionally, the primer can be also fabricated of a biologically absorbable block copolymer, which can be the same or

different in the reservoir and in the primer. In one embodiment, biologically absorbable copolymers that can be used for making any of the stent coating layers include poly(ester amides)(PEA). Optionally, in some other embodiments, condensation copolymers, such as poly(esters) having no amide bonds, can be used instead of PEAs.

- 5 The synthetic techniques that can be used for obtaining both the PEAs and the poly(esters) are described below in the application. Generally, the PEAs are products of reaction between at least one reagent of group A, at least one reagent of group B and reagent C₁ of group C. The poly(esters) are products of reaction between at least one reagent of group A and a reagent C₂ of group C. The precursor-reagents of groups A, B, and C that can be used
- 10 are characterized as follows.

A. Group A Reagents.

- The group A precursor-reagents (hereinafter, "reagents") that can be used for synthesizing the biologically absorbable copolymers according to embodiments of the present invention are summarized in Table 1. The definition used to describe a chemical family to
- 15 which each of the group A reagents belongs is also provided in Table 1.

Table 1. Group A Reagents

No.	Code	Reagent General Formula	Reagent Definition
1.	A ₁	$\begin{array}{c} \text{R}_1 \quad \text{O} \quad \quad \text{O} \quad \text{R}_1 \\ \quad \parallel \quad \quad \parallel \quad \\ \text{H}_2\text{N}-\text{CH}-\text{C}-\text{O}-\text{X}-\text{O}-\text{C}-\text{CH}-\text{NH}_2 \end{array}$	Diol-diamine
2	A ₂	$\begin{array}{c} \text{O} \quad \quad \text{O} \\ \parallel \quad \quad \parallel \\ \text{HO}-\text{R}_2-\text{C}-\text{NH}-\text{Y}-\text{NH}-\text{C}-\text{R}_2-\text{OH} \end{array}$	Amidediol
3	A ₃	HO-X-OH	Diol
4	A ₄	H ₂ N-Y-NH ₂	Diamine

In the general formulae of compounds A₁, A₂, A₃, and A₄ presented in Table 1, the substituents R₁, R₂, X, and Y can be as follows:

R₁ – (a) hydrogen;

(b) methyl ($-\text{CH}_3$);

5 (c) *iso*-propyl ($-i\text{-C}_3\text{H}_7$);

(d) *sec*-butyl ($-\text{sec-C}_4\text{H}_9$);

(e) *iso*-butyl ($-i\text{-C}_4\text{H}_9$); or

(f) benzyl ($-\text{CH}_2\text{C}_6\text{H}_5$);

R₂ – (a) methylene ($-\text{CH}_2-$);

10 (b) ethylene ($-\text{CH}_2\text{CH}_2-$);

(c) methylenemethylene [$-\text{CH}(\text{CH}_3)-$];

(d) straight chained or branched propylene, such as:

(d1) *n*-propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$);

(d2) *iso*-propylene [$-\text{CH}_2\text{CH}(\text{CH}_3)-$]; or

15 (d3) ethylmethylene [$-\text{CH}(\text{CH}_2\text{CH}_3)-$];

(e) straight chained or branched butylene, such as:

(e1) *n*-butylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$),

(e2) *iso*-butylene [$-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$], or

(e3) *sec*-butylene [$-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2-$];

20 (f) straight chained or branched pentylene, such as:

(f1) *n*-pentylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$),

(f2) *iso*-pentylene [$-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$],

(f3) neopentylene [$-\text{CH}[\text{C}(\text{CH}_3)_3]-$],

(f4) 2-methyl-1-butylene [$-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_3)\text{CH}_2-$],

(f5) *sec-iso*-pentylene [$-\text{C}(\text{CH}_3)_2\text{CH}(\text{CH}_3)-$], or

(f6) methylpropylmethylene [$-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3)-$]; or

(g) groups that are present in some amino acids, such as:

5 (g1) methyleneamide (present in asparagine) [$-\text{CH}_2(\text{CONH}_2)-$];

(g2) ethyleneamide (present in glutamine) [$-\text{CH}_2\text{CH}_2(\text{CONH}_2)-$];

(g3) methylmercaptomethylmethylene (present in methionine) [$-\text{CH}_2(\text{CH}_2\text{SCH}_3)-$]; or

(g4) *n*-propyleneamino group ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$) which is derived from 2-pyrrolidine group present (present in proline);

10 X – straight chained or branched aliphatic alkylene group C_nH_{2n} , wherein n is an integer between 2 and 16, e.g., methylene, ethylene, propylene, butylene, amylene (pentylene), hexylene, heptylene, octylene, nonylene, decylene, undecylene, or dodecylene group; and

Y – straight chained or branched aliphatic alkylene group C_2H_4 (ethylene), C_3H_6 (propylene), C_4H_8 (butylene), or C_5H_{10} (pentylene also known as amylene).

15 The reagent A_1 is a diol-diamine that can be synthesized by condensation of two molar equivalents of an amino acid and one molar equivalent of a diol. The synthesis can be carried under the conditions favoring esterification of the amino acid via the amino acid's carboxyl group. The reaction can be conducted under dehydrating conditions which include anhydrous environment and an elevated temperature, for example, about 50°C , and can be catalyzed by a
20 strong acid or base, e.g., *p*-toluenesulfonic acid.

The diol that can be used to make the reagent A_1 has the formula $\text{HO}-\text{X}-\text{OH}$, where X is as defined above. Representative examples of diols that can be used include ethylene

glycol, 1,3-propanediol, 1,4-butane diol, 1,5-pentanediol, 1,6-hexanediol, 1,7-heptanediol, 1,8-octanediol, 1,9-nonanediol, 1,10-decanediol, 1,11-undecanediol, and 1,12-dodecanediol.

The amino acid that can be used to make the reagent A_1 has the formula H_2N-CHR_1-COOH , where R_1 is as defined above. Some amino acids that can be used are summarized in Table 2.

5 Table 2. Amino Acids That Can Be Used for Making the Reagent A_1

No.	R_1	Amino Acid (H_2N-CHR_1-COOH)	
		Formula	Name
1	$-H$	H_2N-CH_2-COOH	glycine
2	$-CH_3$	$\begin{array}{c} CH_3 \\ \\ H_2N-CH-COOH \end{array}$	alanine
3	$-i-C_3H_7$	$\begin{array}{c} CH_3-CH-CH_3 \\ \\ H_2N-CH-COOH \end{array}$	valine
4	$-sec-C_4H_9$	$\begin{array}{c} CH_3-CH_2-CH-CH_3 \\ \\ H_2N-CH-COOH \end{array}$	isoleucine
5	$-i-C_4H_9$	$\begin{array}{c} CH_3 \\ \\ CH_3-CH-CH_2 \\ \\ H_2N-CH-COOH \end{array}$	leucine
6	$C_6H_5CH_2-$	$\begin{array}{c} C_6H_5-CH_2 \\ \\ H_2N-CH-COOH \end{array}$	phenyl alanine
7	$-(CH_2)_2-S-CH_3$	$\begin{array}{c} CH_2-CH_2-S-CH_3 \\ \\ H_2N-CH-COOH \end{array}$	methionine (α -amino- γ -methylmercaptobutyric acid)
8	$-CH_2-C(O)-NH_2$	$\begin{array}{c} CH_2-C(O)-NH_2 \\ \\ H_2N-CH-COOH \end{array}$	asparagine (α -amino-succinamic acid)
9	$-(CH_2)_2-C(O)-NH_2$	$\begin{array}{c} CH_2-CH_2-C(O)-NH_2 \\ \\ H_2N-CH-COOH \end{array}$	glutamine (2-amino-glutaramic acid)

In addition to amino acids listed in Table 2, alternatively other amino acids can be used. One example of such alternative amino acids is proline (2-pyrrolidine carboxylic acid). Other alternative amino acids that can be used include some amino acids having free hydroxyl groups or second carboxyl groups if the free hydroxyl groups or the second carboxyl groups are protected first. The protection is needed so as to avoid interference when reagent A₁ is subsequently reacted with reagents of groups B and C, as discussed above. Examples of the amino acids that can be used after the free hydroxyl or second carboxyl groups are protected include tyrosine, serine, or glutamic acid.

The reagent A₂ is an amidediol that can be synthesized by condensation of two molar equivalents of a hydroxy acid and one molar equivalent of a diamine. The synthesis can be carried under the conditions favoring formation of an amide bond. The reaction can be conducted under dehydrating conditions which include anhydrous environment, and can be catalyzed by a strong base. Simple heating of the neat starting materials with the simultaneous removal of generated water by distillation can also be used.

The diamine that can be used to make the reagent A₂ has the formula H₂N—Y—NH₂, where Y is as defined above. Accordingly, examples of diamines that can be used include 1,4-butanediamine (putrescine) (Y = CH₂CH₂CH₂CH₂). Alternatively, other diamines, such as 1,2-ethanediamine (Y = CH₂CH₂) or 1,5-pentanediamine (cadavarene) (Y = CH₂CH₂CH₂CH₂CH₂) can be used. The hydroxy acid that can be used to make the reagent A₂ has the formula HO—R₂—COOH, where R₂ is as defined above. Some hydroxy acids that can be used are summarized in Table 3.

Table 3. Hydroxy Acids That Can Be Used for Making the Reagent A₂

No.	R ₂	Hydroxy Acid (HO—R ₂ —COOH)	
		Formula	Name
1	—CH ₂ —	HO—CH ₂ —COOH	glycolic (hydroxyacetic) acid
2	—CH ₂ —CH ₂ —	HO—CH ₂ —CH ₂ —COOH	β-hydroxypropionic acid
3	$\begin{array}{c} \text{—CH—} \\ \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{HO—CH—COOH} \end{array}$	lactic (α-hydroxypropionic) acid
4	$\begin{array}{c} \text{—CH—CH}_2\text{—} \\ \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{HO—CH—CH}_2\text{—COOH} \end{array}$	β-hydroxybutyric acid
5	$\begin{array}{c} \text{—CH—} \\ \\ \text{CH}_2\text{—CH}_2\text{—CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—CH}_2\text{—CH}_2 \\ \\ \text{HO—CH—COOH} \end{array}$	α-hydroxyvaleric acid
6	$\begin{array}{c} \text{—CH—CH}_2\text{—} \\ \\ \text{CH}_2\text{—CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—CH}_2 \\ \\ \text{HO—CH—CH}_2\text{—COOH} \end{array}$	β-hydroxyvaleric acid
7	—(CH ₂) ₅ —	HO—(CH ₂) ₅ —COOH	ε-hydroxycaproic acid
8	$\begin{array}{c} \text{—CH—} \\ \\ \text{CH}_3\text{—(CH}_2\text{)}_2\text{—CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—(CH}_2\text{)}_3\text{—CH—COOH} \\ \\ \text{OH} \end{array}$	α-hydroxycaproic acid
8	$\begin{array}{c} \text{—CH—CH}_2\text{—} \\ \\ \text{CH}_3\text{—CH}_2\text{—CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—(CH}_2\text{)}_2\text{—CH—CH}_2\text{—COOH} \\ \\ \text{OH} \end{array}$	β-hydroxycaproic acid
9	$\begin{array}{c} \text{—(CH}_2\text{)}_2\text{—CH—} \\ \\ \text{CH}_3\text{—CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—CH}_2\text{—CH—(CH}_2\text{)}_2\text{—COOH} \\ \\ \text{OH} \end{array}$	δ-hydroxycaproic acid

The reagent A₃ is a common simple diol having the formula HO—X—OH, where X is as defined above; and the reagent A₄ is a common simple diamine having the formula

5 H₂N—Y—NH₂, where Y is as defined above.

B. Group B Reagents.

The group B reagents that can be used for synthesizing the biologically absorbable copolymers according to embodiments of the present invention are summarized in Table 4.

Exemplary definitions used to describe a chemical family to which each of the group B

5 reagents belongs is also provided in Table 4.

Table 4. Group B Reagents

No.	Code	Reagent General Formula	Exemplary Reagent Definition ($R_4 = \text{PEG}$)
1	B ₁	$\begin{array}{c} R_1 \quad O \quad \quad O \quad R_1 \\ \quad \quad \quad \quad \\ H_2N-CH-C-O-R_4-O-C-CH-NH_2 \end{array}$	PEG-diester-diamine
2	B ₂	$\begin{array}{c} O \quad \quad O \\ \quad \quad \\ HO-R_2-C-NH-R_4-NH-C-R_2-OH \end{array}$	PEG-amidediol
3	B ₃	$HO-R_4-OH$	PEG-diol
4	B ₄	$H_2N-R_4-NH_2$	PEG-diamine

In general formulae of compounds B₁, B₂, B₃, and B₄ presented in Table 4, the substituents R₁ and R₂ are as defined above. One example of the R₄ moiety that can be used is a moiety derived from poly(ethylene glycol) (PEG). Alternatively, other biologically beneficial moieties can be used as R₄, for example, moieties derived from poly(propylene glycol) (PPG), random or block copolymers of PEG and PPG, hyaluronic acid, poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropylmethacrylamide), or cellulose.

The reagent B₁ can be a PEG-diester-diamine adduct (i.e., when R₄ = PEG) that can be synthesized by condensation of two molar equivalents of an amino acid and one molar equivalent of PEG. The synthesis can be carried under the conditions favoring esterification of the amino acid via the carboxyl group. The reaction can be conducted under dehydrating conditions which include anhydrous environment and an elevated temperature, for example,

about 50°C, and can be catalyzed by a strong acid or base, e.g., *p*-toluenesulfonic acid. To make the reagent B₁, PEG having molecular weight between about 100 and 4,000 Daltons, for example, about 300 Daltons, can be used. Any amino acid listed in Table 2 can be used.

Alternatively, other amino acids can be used, for example, tyrosine, serine, or glutamic acid, if
 5 free hydroxyl groups of tyrosine and serine or the second carboxyl group of glutamic acid are protected so as not to interfere when reagent B₁ is subsequently reacted with reagents of groups A and C, as discussed above.

The reagent B₂ can be a PEG-amidediol that can be synthesized by condensation of two molar equivalents of a hydroxy acid and one molar equivalent of a PEG-diamine. The
 10 synthesis can be carried under the conditions favoring formation of an amide bond. The reaction can be conducted under dehydrating conditions which include anhydrous environment, and can be catalyzed by a strong base, or prepared from neat reagents by heating at high temperature with the simultaneous removal of generated water, e.g., the removal of water by distillation. Any hydroxy acid listed in Table 3 can be used. PEG terminated with
 15 amino groups on both ends (PEG-diamine reagent B₄) can be obtained from Huntsman Chemical Co. of Houston, Texas under the trade name JEFFAMINE.

C. Group C Reagents.

The group C reagents that can be used for synthesizing the biologically absorbable copolymers according to embodiments of the present invention are summarized in Table 5.
 20 The definition used to describe a chemical family to which each of the group C reagents belongs is also provided in Table 5.

Table 5. Group C Reagents

No.	Code	Reagent General Formula	Reagent Definition
1	C ₁	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{R}_3-\text{C}-\text{OH} \end{array}$	Dicarboxylic acid
2	C ₂	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{PEG}-\text{C}-\text{OH} \end{array}$	PEG-dicarboxylic acid

In general formula of compound C₁ presented in Table 5, the substituent R₃ is simply a covalent bond, or a straight chained or branched aliphatic alkylene group C_nH_{2n}, wherein n is an integer having a value between 0 and 12, e.g. a single bond (n = 0), methylene, ethylene, propylene, butylene, amylene (pentylene), hexylene, heptylene, octylene, nonylene, decylene, undecylene, or dodecylene group, or an aromatic group, e.g., phenyl or *para*-phenylene.

Some examples of dicarboxylic acids that can be used as the reagent C₁ are summarized in Table 6.

Table 6. Dicarboxylic Acids That Can Be Used As the Reagent C₁

No.	R ₃	Dicarboxylic Acid (HOOC—R ₃ —COOH)	
		Formula	Name
1	—(CH ₂) ₂ —	HOOC—(CH ₂) ₂ —COOH	succinic (butanedioic) acid
2	—(CH ₂) ₄ —	HOOC—(CH ₂) ₄ —COOH	adipic (hexanedioic) acid
3	—(CH ₂) ₈ —	HOOC—(CH ₂) ₈ —COOH	sebacic (decanedioic) acid
4	(<i>p</i>)—C ₆ H ₄ —	HOOC—(<i>p</i>)C ₆ H ₄ —COOH	terephthalic (1,4-benzene dicarboxylic) acid

In addition to the dicarboxylic acids listed in Table 6, examples of other dicarboxylic acids that can be also used include oxalic acid, malonic acid, glutaric acid, pimelic acid, suberic acid, or azelaic acid. As mentioned above, to synthesize the PEAs, at least one reagent of group A can be reacted with at least one reagent of group B and reagent C₁. To make the poly(esters), at least one reagent of group A can be reacted with reagent C₂.

One of several routes can be utilized to synthesize the polymers of this invention. Those having ordinary skill in the art can appreciate that the reagents of groups A, B, and C may themselves contain hydrolysable bonds, i.e. ester or amide bonds. These reagents can be then polymerized, the polymerization creating additional bonds that may be both ester and amide bonds, only amide bonds, or only ester bonds. Given that the reagents can be obtained separately, the types of polymers formed during the polymerization can belong to one of the following four categories (A), (B), (C), or (D):

(A) Polymers in which amide bonds are formed between reagents which themselves contain ester bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

(1) A₁, B₁ and C₁ (A₁-B₁-C₁);

(2) A₁, B₄ and C₁ (A₁-B₄-C₁);

(3) A₄, B₁ and C₁ (A₄-B₁-C₁); and

(4) A₁ and C₂ (A₁-C₂).

(B) Polymers in which amide bonds are formed between reagents which themselves contain neither ester nor amide bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

(1) A_4 , B_4 and C_1 (A_4 - B_4 - C_1); and

5 (2) A_4 and C_2 (A_4 - C_2).

(C) Polymers in which both ester and amide bonds are formed between the reagents. The subunits themselves may contain ester and amide bonds, only ester bonds, only amide bonds, or neither ester nor amide bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

10 (1) A_1 , B_2 and C_1 (A_1 - B_2 - C_1);

(2) A_1 , B_3 and C_1 (A_1 - B_3 - C_1);

(3) A_2 , B_1 and C_1 (A_2 - B_1 - C_1);

(4) A_2 , B_4 and C_1 (A_2 - B_4 - C_1);

(5) A_3 , B_1 and C_1 (A_3 - B_1 - C_1);

15 (6) A_3 , B_4 and C_1 (A_3 - B_4 - C_1);

(7) A_4 , B_2 and C_1 (A_4 - B_2 - C_1); and

(8) A_4 , B_3 and C_1 (A_4 - B_3 - C_1).

(D) Polymers in which ester bonds are formed between reagents which themselves may contain amide bonds, or neither amide nor ester bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

(1) A_2 , B_2 and C_1 (A_2 - B_2 - C_1);

5 (2) A_2 , B_3 and C_1 (A_2 - B_3 - C_1);

(3) A_2 and C_2 (A_2 - C_2);

(4) A_3 , B_2 and C_1 (A_3 - B_2 - C_1);

(5) A_3 , B_3 and C_1 (A_3 - B_3 - C_1); and

(6) A_3 and C_2 (A_3 - C_2).

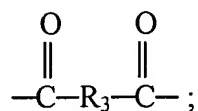
10 Due to the types of bonds being formed, and the types of bonds present, those having ordinary skill in the art will understand that the polymerization scheme need be adjusted for each category in order to form the desired polymer while not hydrolyzing or degrading the existing bonds in the reagents, or creating uncontrolled, mixed species. Some examples of the synthesis of particular polymers are provided below in the "Examples" section of the present
15 application.

As a result of the synthesis, biologically absorbable PEAs having a general formula (A) or poly(esters) having a general formula (B) can be obtained:

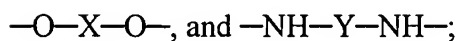
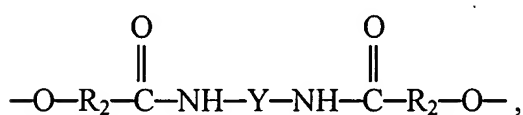
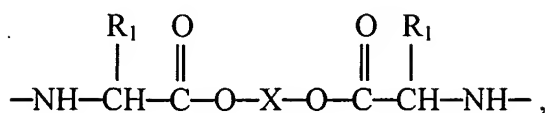


20 wherein:

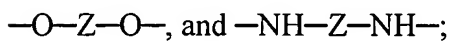
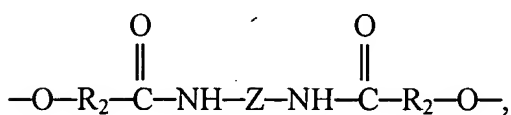
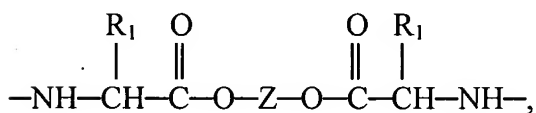
M is a moiety represented by the structure



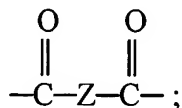
P is a moiety including:



Q is a moiety selected from a group consisting of:



M₁ is a moiety represented by the structure



R₁, R₂, R₃, X and Y are substituents and moieties as defined above;

Z is a moiety that can be derived from a compound selected from a group consisting of

poly(ethylene glycol)(PEG), poly(propylene glycol) (PPG), random or block copolymers of PEG and PPG, hyaluronic acid, poly(2-hydroxyethyl methacrylate), poly(3-

hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone, and cellulose; and

m, n, and p are integers where the value of m can be between 5 and 1,800, the value of n can be between 1 and 800 and the value of p can be between 4 and 1,500.

5 Any layer of the stent coating can contain any amount of the biologically absorbable copolymers described above, or a blend of more than one of such copolymers. If less than 100% of the layer is made of the biologically absorbable copolymers, or blends thereof, described above, alternative polymers can comprise the balance. Examples of the alternative polymers that can be used include polyacrylates, such as poly(butyl methacrylate), poly(ethyl
10 methacrylate), and poly(ethyl methacrylate-co-butyl methacrylate), and fluorinated polymers and/or copolymers, such as poly(vinylidene fluoride) and poly(vinylidene fluoride-co-hexafluoro propene), poly(N-vinyl pyrrolidone), poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-
15 lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), co-poly(ether-esters), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin
20 copolymers, vinyl halide polymers and copolymers (such as polyvinyl chloride), polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), copolymers of vinyl monomers with each other and olefins, e.g., poly(ethylene-co-

vinyl alcohol) (EVAL), ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

Representative examples of some solvents suitable for making the stent coatings include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), cyclohexanone, xylene, toluene, acetone, *i*-propanol, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, *n*-butyl acetate, and dioxane. Some solvent mixtures can be used as well. Representative examples of the mixtures include:

- (1) DMAC and methanol (e.g., a 50:50 by mass mixture);
 - (2) water, *i*-propanol, and DMAC (e.g., a 10:3:87 by mass mixture);
 - (3) *i*-propanol, and DMAC (e.g., 80:20, 50:50, or 20:80 by mass mixtures);
 - (4) acetone and cyclohexanone (e.g., 80:20, 50:50, or 20:80 by mass mixtures);
 - (5) acetone and xylene (e.g. a 50:50 by mass mixture);
 - (6) acetone, FLUX REMOVER AMS, and xylene (e.g., a 10:50:40 by mass mixture);
- and
- (7) 1,1,2-trichloroethane and chloroform (e.g., a 80:20 by mass mixture).

FLUX REMOVER AMS is trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Texas comprising about 93.7% of a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance of methanol, with trace amounts of nitromethane. Those having ordinary skill in the art will
 5 select the solvent or a mixture of solvents suitable for a particular polymer being dissolved.

The therapeutic substance which can be used in the reservoir layer can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The therapeutic substance may include small molecule substances, peptides, proteins, oligonucleotides, and the like. The therapeutic substance could be designed, for example, to
 10 inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis.

Examples of therapeutic substances that can be used include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich of Milwaukee, Wisconsin, or COSMEGEN available from Merck).
 15 Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I₁, actinomycin X₁, and actinomycin C₁. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL[®] by Bristol-Myers Squibb
 20 Co., Stamford, Conn.), docetaxel (e.g. Taxotere[®], from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin[®] from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin[®] from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such

antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX (Biogen, Inc., Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten[®] and Capozide[®] from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil[®] and Prinzide[®] from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor[®] from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus, dexamethasone, and rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin.

The coatings and methods of the present invention have been described with reference to a stent, e.g., a balloon expandable or self-expandable stent. The use of the coating is not limited to stents, and the coating can also be used with a variety of other medical devices, such as implantable medical devices. Examples of the implantable medical device, that can be used in conjunction with the embodiments of this invention include stent-grafts, grafts (e.g., aortic grafts), catheters, guidewires, artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, axius coronary shunts and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt-chromium alloys (e.g., ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, tantalum-based alloys, nickel-titanium alloy, platinum, platinum-based alloys such as, e.g., platinum-iridium alloy, iridium, gold, magnesium, titanium, titanium-based alloys, zirconium-based alloys, or combinations thereof. Devices made from bioabsorbable or biostable polymers can also be used with the embodiments of the present invention. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

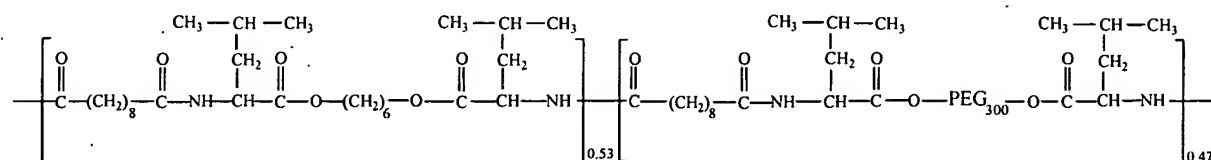
Medical devices can be also made from the materials of the invention. Moreover, the polymers can be used for a variety of medical applications, including particles for drug delivery to embolize blood vessels. The polymers of the present invention can have a variety of medical applications, including the treatment of stenosis, restenosis, and cancer.

3. Examples.

The following examples are provided to further illustrate embodiments of the present invention.

Example 1

5 A copolymer having formula (III) can be synthesized and used in practice of the invention:



(III)

The copolymer (III) is a product of copolymerization of reagents A₁, B₁, and C₁. A₁ can be a diol-diamine shown in Table 1 where R₁ is *i*-C₄H₉ and X is (CH₂)₆. In other words, A₁ can be synthesized by condensation of leucine with 1,6-hexanediol. B₁ can be a PEG-diester-diamine shown in Table 4 where R₁ is *i*-C₄H₉ and PEG₃₀₀ symbolizes a moiety derived from poly(ethylene glycol) having molecular weight of about 300 Daltons. In other words, B₁ can be synthesized by condensation of leucine with poly(ethylene glycol) having molecular weight of about 300 Daltons. C₁ can be a dicarboxylic acid shown in Table 5 where R₃ is (CH₂)₈ (sebacic acid, which is also shown in Table 6).

To synthesize copolymer (III), about 30.8 ml dry triethylamine (about 0.22 mole), in about 55 ml dry solvent N,N'-dimethylacetamide, at room temperature, can be added to a mixture of:

(a) about 36.37 g (about 0.053 mole) di-*para*-toluenesulfonic acid salt of *bis*-(L-leucine)-1,6-hexylene diester;

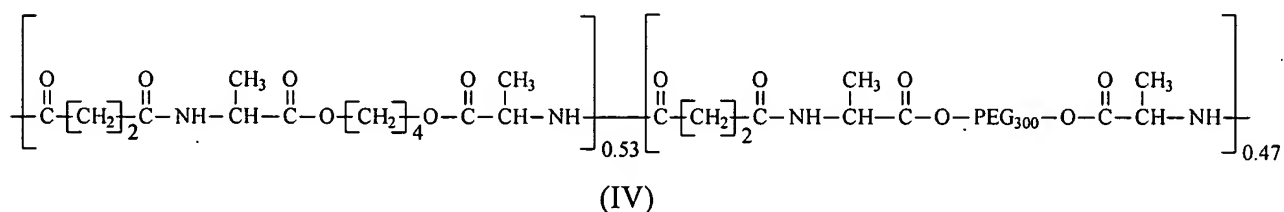
(b) about 39.3 g (about 0.047 mole) di-*para*-toluenesulphonic acid salt of *bis*-(L-leucine)-PEG300 diester; and

5 (c) about 44.4 g (about 0.1 mole) di-*para*-nitrophenyl sebacinate.

The mixture can be stirred until full dissolution and then the temperature can be raised to about 80°C. After stirring for about 24 hours, the viscous mixture can be cooled to room temperature, diluted with about 100 ml ethanol and precipitated into an excess of water. The separated polymer can be thoroughly washed with water, spread thinly onto a TEFLON pan,
 10 and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

Example 2

A copolymer having formula (IV) can be synthesized and used in practice of the invention.



15 The copolymer (IV) is a product of copolymerization of reagents A₁, B₁, and C₁. A₁ can be a diol-diamine shown in Table 1, where R₁ is CH₃ and X is (CH₂)₄. In other words, A₁ can be synthesized by condensation of alanine with 1,4-butanediol. B₁ can be a PEG-diester-diamine shown in Table 4 where R₁ is *i*-C₄H₉ and PEG₃₀₀ symbolizes a moiety derived from

poly(ethylene glycol) having molecular weight of about 300 Daltons. In other words, B₁ can be synthesized by condensation of alanine with poly(ethylene glycol) having molecular weight of about 300 Daltons. C₁ can be a dicarboxylic acid shown in Table 5 where R₃ is (CH₂)₂ (succinic acid, which is also shown in Table 6).

5 To synthesize copolymer (IV), about 30.8 ml dry triethylamine (about 0.22 mole), in about 55 ml dry solvent N,N'-dimethylacetamide, at room temperature, can be added to a mixture of:

(a) about 30.43 g (about 0.053 mole) di-*para*-toluenesulfonic acid salt of *bis*-(L-alanine)-1,4-butylene diester;

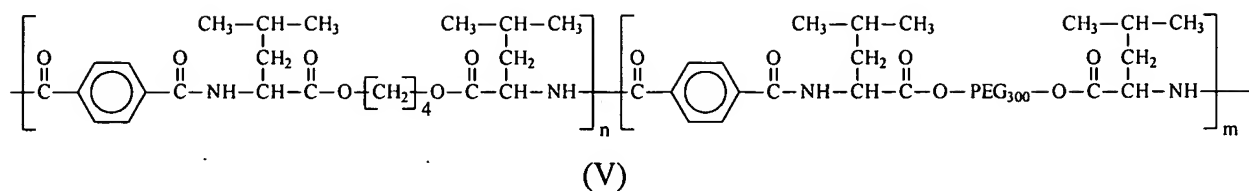
10 (b) about 36.86 g (about 0.047 mole) di-*para*-toluenesulphonic acid salt of *bis*-(L-alanine)-PEG300 diester; and

(c) about 36.0 g (about 0.1 mole) di-*para*-nitrophenyl succinate.

The mixture can be stirred until full dissolution and then the temperature can be raised to about 80°C. After stirring for about 24 hours, the viscous mixture can be cooled to room
15 temperature, diluted with about 100 ml ethanol and precipitated into an excess of water. The separated polymer is thoroughly washed with water, spread thinly into a TEFLON pan, and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

Example 3

A copolymer having formula (V) can be synthesized and used in practice of the
20 invention.

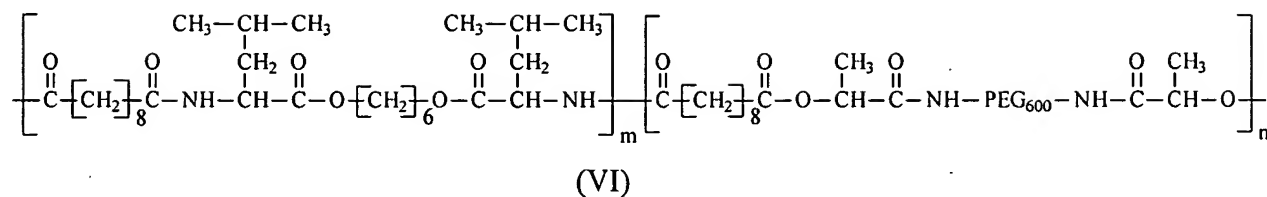


The copolymer (V) is a product of copolymerization of reagents A₁, B₁, and C₁. A₁ can be a diol-diamine shown in Table 1 where R₁ is *i*-C₄H₉ and X is (CH₂)₄. In other words, A₁ can be synthesized by condensation of leucine with 1,4-butanediol. B₁ can be a PEG-diester-diamine shown in Table 4 where R₁ is *i*-C₄H₉ and PEG₃₀₀ symbolizes a moiety derived from poly(ethylene glycol) having molecular weight of about 300 Daltons. In other words, B₁ can be synthesized by condensation of leucine with poly(ethylene glycol) having molecular weight of about 300 Daltons. C₁ can be a dicarboxylic acid shown in Table 5 where R₃ is *para*-C₆H₄ (terephthalic acid, which is also shown in Table 6).

The copolymer (V) can be obtained using the same synthetic technique as described in Example 2 for copolymer (IV), except di-*para*-nitrophenylterephthalate can be used to make the copolymer (V), instead of di-*para*-nitrophenyl succinate. In copolymer (V), the value of n can be between about 0.64 and about 0.97 and the value of m can be between about 0.03 and about 0.36, where m + n = 1.

Example 4

A copolymer having formula (VI) can be synthesized and used in practice of the invention.



The copolymer (VI) is a product of copolymerization of reagents A₁, B₂, and C₁. A₁ can be a diol-diamine shown in Table 1 where R₁ is *i*-C₄H₉ and X is (CH₂)₆. In other words, A₁ can be synthesized by condensation of leucine with 1,6-hexanediol. B₂ can be a PEG-amidediol shown in Table 4 where R₂ is methylenemethylene CH(CH₃).

In other words, B₂ can be synthesized by condensation of lactic acid with PEG-diamine shown as reagent B₄ in Table 4. PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG₆₀₀.

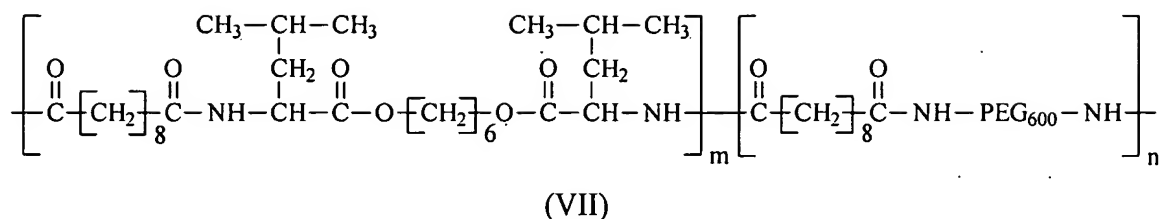
For example, JEFFAMINE ED-600 available from Huntsman Corp. can be used. JEFFAMINE ED-600 is a trade name of O,O'-bis-[(2-aminopropyl) poly(propylene glycol)-block-poly(ethylene glycol)-block-poly(propylene glycol)] which is a polyether diamine with a polyalkylene oxide backbone. The molecular weight of JEFFAMINE ED-600 is about 600 Daltons.

C₁ can be a dicarboxylic acid shown in Table 5 where R₃ is (CH₂)₈ (sebacic acid, which is also shown in Table 6). In copolymer (VI), the value of n can be between about 0.60 and about 0.93 and the value of m can be between about 0.07 and about 0.40 (m + n = 1).

Example 5

A copolymer having formula (VII) can be synthesized and used in practice of the

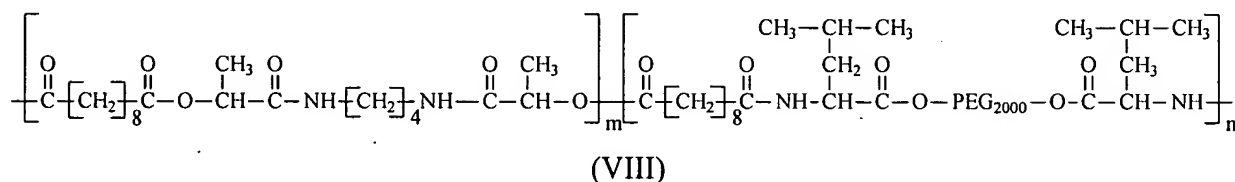
invention.



The copolymer (VII) can be synthesized in same way as the copolymer (VI) of Example 4, except instead of a reagent B₂ (e.g., PEG-amidediol), reagent B₄ (e.g., PEG-diamine) shown in Table 4 can be used. In copolymer (VII), the value of n can be between about 0.59 and about 0.96 and the value of m can be between about 0.04 and about 0.41, where m + n = 1.

Example 6

A copolymer having formula (VIII) can be synthesized and used in practice of the invention.



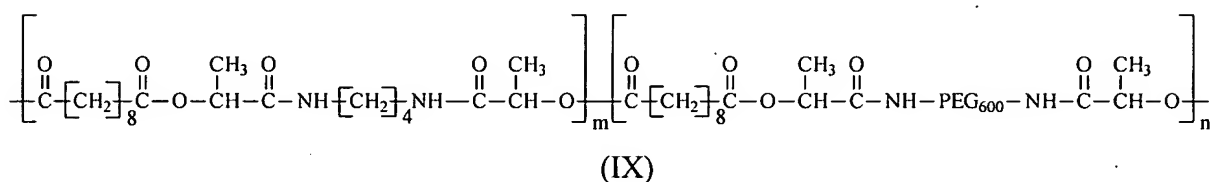
The copolymer (VIII) is a product of copolymerization of reagents A₂, B₁, and C₁. A₂ can be an amidediol shown in Table 1 where R₂ is methylmethylene CH(CH₃) and Y is (CH₂)₄. In other words, A₂ can be synthesized by condensation of lactic acid with the 1,4-diamino butane (putrescine).

B₁ can be a PEG-diester-diamine shown in Table 4 where R₁ is *i*-C₄H₉. In other words, B₁ can be synthesized by condensation of leucine with poly(ethylene glycol) having molecular weight of about 2,000 Daltons, which is symbolized by the abbreviation PEG₂₀₀₀.

C₁ can be a dicarboxylic acid shown in Table 5 where R₃ is (CH₂)₈ (sebacic acid, which is also shown in Table 6). In copolymer (VIII), the value of n can be between about 0.86 and about 0.99 and the value of m can be between about 0.01 and about 0.14, where m + n = 1.

Example 7

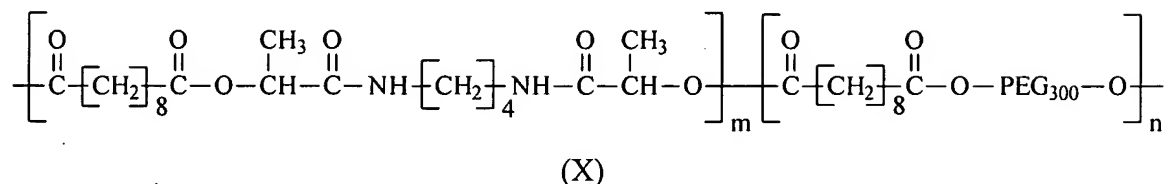
A copolymer having formula (IX) can be synthesized and used in practice of the invention.



The copolymer (IX) can be synthesized in same way as the copolymer (VIII) of Example 6, except instead of a reagent B₁ (PEG-diester-diamine), reagent B₂ (PEG-amidediol) shown in Table 4 can be used, where R₂ is methylethylene CH(CH₃). In other words, B₂ can be synthesized by condensation of lactic acid with PEG-diamine shown as reagent B₄ in Table 4. PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG₆₀₀. In copolymer (IX), the integer value of n can be between about 0.69 and about 0.98 and the value of m can be between about 0.02 and about 0.31, where m + n = 1.

Example 8

A copolymer having formula (X) can be synthesized and used in practice of the invention.



- 5 The copolymer (X) can be synthesized in same way as the copolymer (IX) of Example 7, except instead of a reagent B₂ (e.g., PEG-amidediol), a reagent B₃ shown in Table 4, (HO—R₄—OH), for example, PEG-diol, can be used. PEG-diol can be based on poly(ethylene glycol) having molecular weight of about 300 Daltons, which is symbolized by the abbreviation PEG₃₀₀.
- 10 A₂ and B₃ reagents can be combined and reacted first to form an A₂-B₃ adduct, followed by adding a C₁ reagent and completing polycondensation. The conditions for the synthesis can be determined by those having ordinary skill in the art. For example, the final step of the reaction (reacting C₁ with the A₂-B₃ adduct) can be conducted in the presence of a coupling agent such as carbodiimide.
- 15 Optionally, instead of a C₁ diacid, a dichloride of the diacid can be used, for instance, sebacyl dichloride. In copolymer (X), the value of n can be between about 0.54 and about 0.96 and the value of m can be between about 0.04 and about 0.46, where m + n = 1.

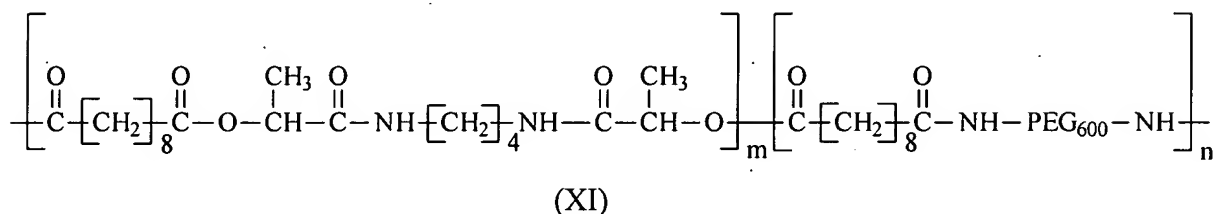
Alternative versions of the copolymer (X) can be also synthesized to make the copolymer (X) harder. For example, an amino acid with shorter R₂ group or a shorter chain

diamine (e.g., ethanediamine instead of 1,4-butanediamine) can be used for preparing the reagent A₂.

Other possible methods of increasing the hardness of the copolymer (X) include using a shorter dicarboxylic acid C₁ (e.g., adipic acid instead of sebacic acid), or using PEG with lower molecular weight, or reducing the proportion of the PEG-containing units in the overall copolymer (X).

Example 9

A copolymer having formula (XI) can be synthesized and used in practice of the invention.



10

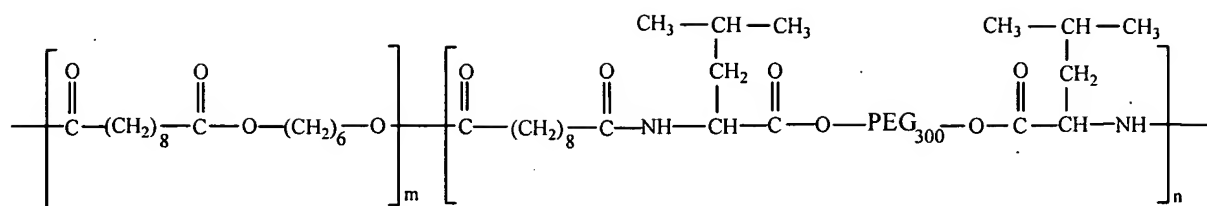
The copolymer (XI) can be synthesized in same way as the copolymer (X) of Example 9, except instead of a reagent B₃ (e.g., PEG-diol), reagent B₄ (such as PEG-diamine) shown in Table 4 can be used. PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG₆₀₀. In copolymer (XI), the value of n can be between about 0.03 and about 0.35 and the value of m can be between about 0.97 and about 0.65, where m + n = 1.

15

Example 10

A copolymer having formula (XII) can be synthesized and used in practice of the

invention.



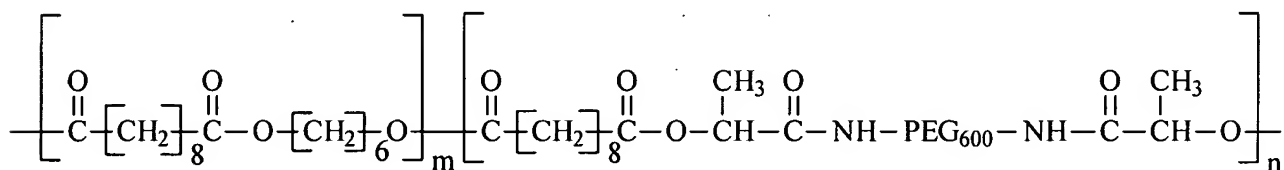
(XII)

The copolymer (XII) can be synthesized in same way as the copolymer (VIII) of

- 5 Example 6, except instead of a reagent A₂ (amidediol), a reagent A₃ (diol) shown in Table 1 can be used, where X is (CH₂)₆. In other words, 1,6-hexanediol can be used as the reagent A₃. A poly(ethylene glycol) moiety having molecular weight of about 300 Daltons can comprise a part of copolymer (XII), which is symbolized by the abbreviation PEG₃₀₀. In copolymer (XII), the value of n can be between about 0.98 and about 0.71 and the value of m can be
- 10 between about 0.02 and about 0.29, where m + n = 1.

Example 11

A copolymer having formula (XIII) can be synthesized and used in practice of the invention.



(XIII)

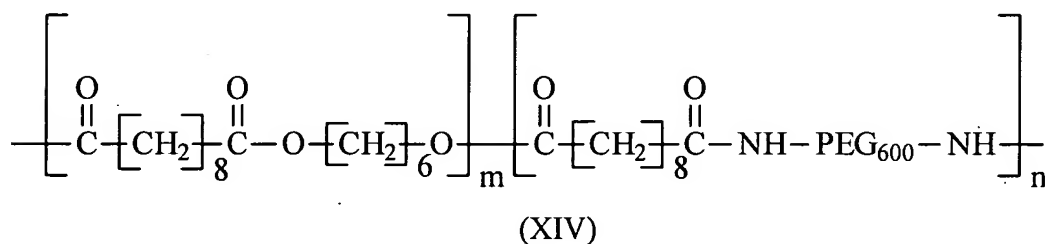
- 15 The copolymer (XIII) can be synthesized in same way as the copolymer (XII) of Example 10, except instead of a reagent B₁ (such as PEG-diester-diamine), a reagent B₂ (e.g.,

PEG-amidediol) shown in Table 4 can be used, where R₂ is methylenemethylene CH(CH₃). In other words, B₂ can be synthesized by condensation of lactic acid with PEG-diamine shown as reagent B₄ in Table 4. PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG₆₀₀.

- 5 In copolymer (XIII), the value of n can be between about 0.98 and about 0.76 and the value of m can be between about 0.02 and about 0.24, where m + n = 1.

Example 12

A copolymer having formula (XIV) can be synthesized and used in practice of the invention.



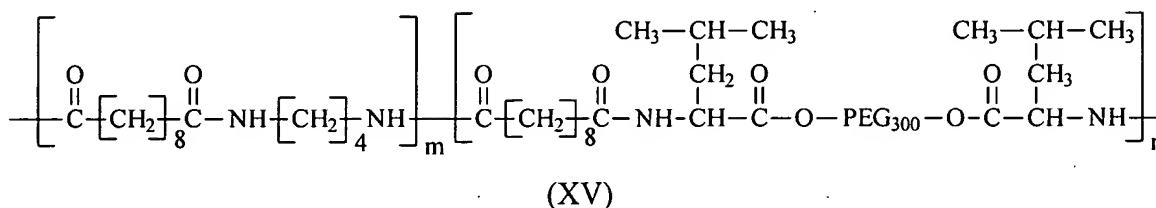
10

- The copolymer (XIV) can be synthesized in same way as the copolymer (XIII) of Example 11, except instead of a reagent B₂ (such as PEG-amidediol), a reagent B₄ (e.g., PEG-diamine), shown in Table 4 can be used. PEG-diamine can be based on poly(ethylene glycol) having molecular weight between about 300 and about 2,400 Daltons, for example, about 600 Daltons, which is symbolized by the abbreviation PEG₆₀₀. Reagent A₃ (1,6-hexanediol) and reagent C₁ (sebacic acid) can be combined and reacted first to form an A₃-C₁ adduct, followed by adding reagent B₄ and completing polycondensation. To facilitate the formation of the A₃-C₁ adduct, sebacyl dichloride can be used as the C₁ reagent instead of sebacic acid. The conditions for the synthesis can be determined by those having ordinary skill in the art.
- 15

In copolymer (XIV), the value of n can be between about 0.98 and about 0.73 and the value of m can be between about 0.02 and about 0.27, where $m + n = 1$.

Example 13

5 A copolymer having formula (XV) can be synthesized and used in practice of the invention.



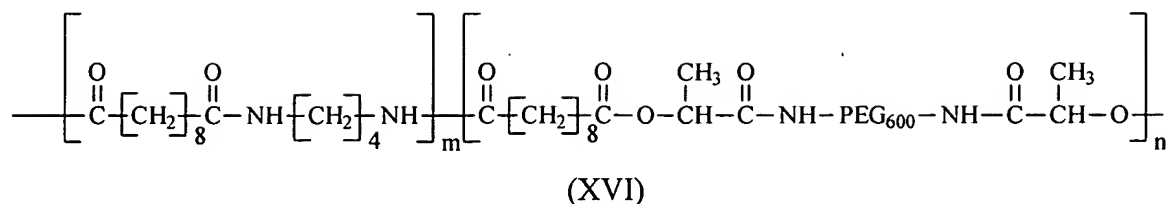
The copolymer (XV) can be synthesized in same way as the copolymer (VIII) of Example 6, except instead of a reagent A_2 (amidediol), a reagent A_4 (diamine) shown in Table 1 can be used, where Y is $(\text{CH}_2)_4$.

10 In other words, putrescine can be used as the reagent A_4 . A poly(ethylene glycol) moiety having molecular weight between about 300 Daltons and about 4,000 Daltons, for example, about 300 Daltons can comprise a part of copolymer (XV), which is symbolized by the abbreviation PEG_{300} .

15 In copolymer (XV), the value of n can be between about 0.98 and about 0.73 and the value of m can be between about 0.02 and about 0.27, where $m + n = 1$.

Example 14

A copolymer having formula (XVI) can be synthesized and used in practice of the invention.



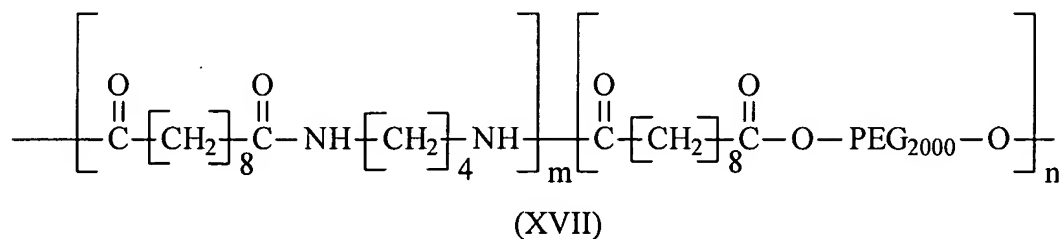
The copolymer (XVI) can be synthesized in same way as the copolymer (IX) of Example 7, except instead of a reagent A₂ (amidediol), a reagent A₄ (diamine) shown in Table 1 can be used, where Y is (CH₂)₄. In other words, putrescine can be used as the reagent A₄.

- 5 A poly(ethylene glycol) moiety having molecular weight between about 300 Daltons and about 4,000 Daltons, for example, about 600 Daltons can comprise a part of copolymer (XVI), which is symbolized by the abbreviation PEG₆₀₀.

In copolymer (XVI), the value of n can be between about 0.98 and about 0.77 and the value of m can be between about 0.02 and about 0.23, where m + n = 1.

10 Example 15

A copolymer having formula (XVII) can be synthesized and used in practice of the invention.



- 15 The copolymer (XVII) can be synthesized in same way as the copolymer (X) of Example 8, except instead of a reagent A₂ (amidediol), a reagent A₄ (diamine) shown in Table

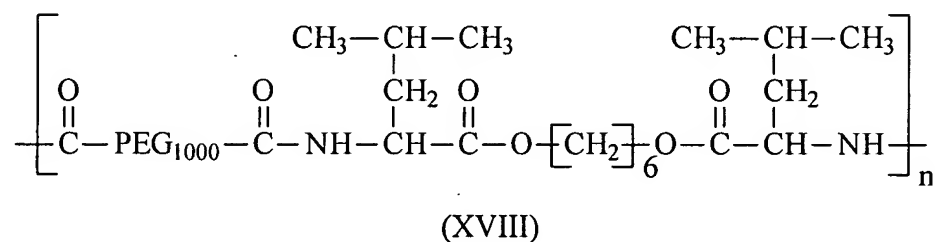
1 can be used, where Y is $(\text{CH}_2)_4$. In other words, putrescine can be used as the reagent A₄.

A poly(ethylene glycol) moiety having molecular weight between about 300 Daltons and about 4,000 Daltons, for example, about 2,000 Daltons can comprise a part of copolymer (XVII), which is symbolized by the abbreviation PEG₂₀₀₀.

5 In copolymer (XVII), the value of n can be between about 0.995 and about 0.91 and the value of m can be between about 0.005 and about 0.09, where $m + n = 1$.

Example 16

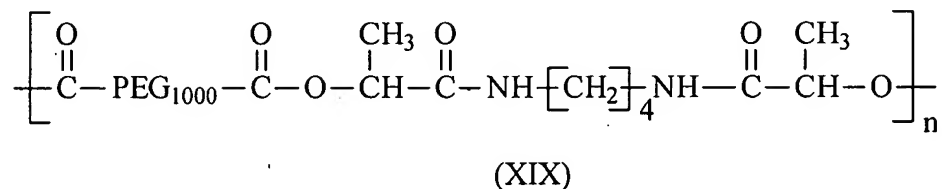
A copolymer having formula (XVIII) can be synthesized and used in practice of the invention.



To synthesize the copolymer (XVIII), reagents A₁ and C₂, can be combined in the molar ratio of about 1:1 and copolymerized. The conditions for the synthesis can be determined by those having ordinary skill in the art. A₁ can be a diol-diamine shown in Table 1 where R₁ is *i*-C₄H₉ and X is (CH₂)₆. In other words, A₁ can be synthesized by condensation of leucine with 1,6-hexanediol. C₂ can be a PEG-dicarboxylic acid shown in Table 5, derived from poly(ethylene glycol) having molecular weight of about 1,000 Daltons, which is symbolized by the abbreviation PEG₁₀₀₀. A total molecular weight of the copolymer (XVIII) can be between about 20,000 Daltons and about 50,000 Daltons. The value of the integer n can be between about 14 and 360.

Example 17

A copolymer having formula (XIX) can be synthesized and used in practice of the invention.

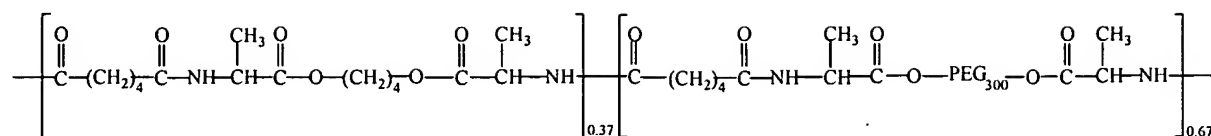


- 5 The copolymer (XIX) can be synthesized in same way as the copolymer (XVIII) of Example 16, except instead of a reagent A₁ (diol-diamine), a reagent A₂ (amidediol) shown in Table 1 can be used, where R₂ is methyldimethylene CH(CH₃) and Y is (CH₂)₄. In other words, A₂ can be synthesized by condensation of lactic acid with putrescine. C₂ can be a PEG-dicarboxylic acid shown in Table 5, derived from poly(ethylene glycol) having molecular
- 10 weight of about 1,000 Daltons, which is symbolized by the abbreviation PEG₁₀₀₀.

A total molecular weight of the copolymer (XIX) can be between about 20,000 Daltons and about 50,000 Daltons. The value of the integer n can be between about 15 and 390.

Example 18

- 15 Co-poly- {[N,N'-adipoyl-bis-(L-alanine)-1,4-butylene diester]_{0.37}-[N,N'-adipoyl-bis-(L-alanine)-PEG300 diester]_{0.67}} having formula (XX) can be synthesized and used in practice of the invention. This copolymer belongs to category (A), type A₁-B₁-C₁, described above.



(XX)

To synthesize the copolymer (XX), about 41 ml (about 0.293 mole) dry triethylamine in about 75 ml dry solvent N,N'-dimethylacetamide, at room temperature, can be added to a mixture of:

(a) about 28.64 g (about 0.0497 mole) di-*para*-toluenesulfonic acid salt of *bis*-(L-alanine)-1,4-butylene diester;

(b) about 65.57 g (about 0.0834 mole) di-*para*-toluenesulphonic acid salt of *bis*-(L-alanine)-PEG300 diester; and

(c) about 51.62 g (about 0.1331 mole) di-*para*-nitrophenyl adipate.

The mixture can be stirred until full dissolution and then the temperature can be raised to about 80°C. After stirring for about 24 hours, the viscous mixture can be cooled to room temperature, diluted with about 100 ml ethanol and precipitated into an excess of water. The separated polymer can be thoroughly washed with water, spread thinly onto a TEFLON pan, and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

As amide bonds are formed in the presence of existing ester bonds, mild conditions need be used, as understood by those having ordinary skill in the art. For example, polymerization techniques using good leaving groups such as *para*-nitrophenol or carboxyl

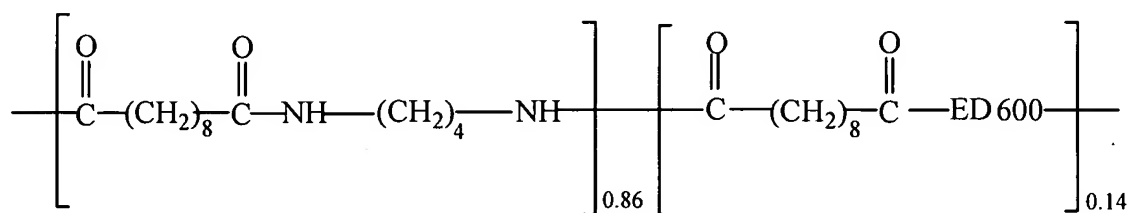
groups activated by carbodiimides can be used. In this invention, the range of stoichiometries can be determined by the desired mass content of PEG.

For example, the final polymer can contain between about 5 mass % and about 50 mass % of PEG. For copolymer (XX), this corresponds to molar ratios of the two blocks of (alanine/butanediol-adipic acid) (A_1-C_1 blocks) and (alanine/PEG-adipic acid) (B_1-C_1 blocks) between about 0.94:0.06 and about 0.12:0.88.

Example 19

Co-poly- $\{[N,N'$ -sebacyl-1,4-butylene diamide] $_{0.86}$ - $[N,N'$ -sebacyl-(ED-600) diamide] $_{0.14}\}$ having formula (XXI) can be synthesized and used in practice of the invention.

10 This copolymer belongs to category (B), type ($A_4-B_4-C_1$), described above.



(XXI)

In formula (XXI), "ED-600" is an abbreviation symbolizing JEFFAMINE ED-600 polymer described above (see Example 4).

15 To synthesize the copolymer (XXI), about 104 ml (about 0.744 mole) dry triethylamine in about 65 ml dry solvent N,N' -dimethylacetamide, at room temperature, can be added to a mixture of:

(a) about 23.38 g (about 0.266 mole) dry 1,4-diaminobutane; and

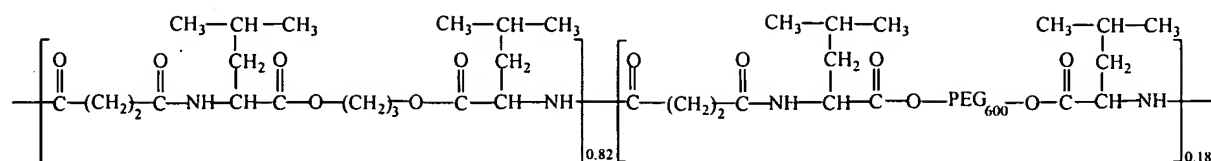
(b) about 25 g (about 0.0417 mole) dry ED-600.

The mixture can be stirred, under a nitrogen atmosphere at room temperature, until full dissolution. The mixture can be cooled in ice water and about 80.75 g (about 0.338 mole) sebacoyl chloride can be added dropwise with stirring. The solution can be allowed to come to ambient temperature with stirring stirred continued overnight. The viscous mixture can then be precipitated into an excess of water. The separated polymer can be thoroughly washed with water, spread thinly into a TEFLON pan, and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

As only amide bonds are present, without any other hydrolysable groups, harsher synthetic conditions can be used for this category as understood by those having ordinary skill in the art. For example, acid chlorides can be used. The mass contents of PEG in the final copolymer (XXI) can be between about 5 mass % and about 50 mass %. For copolymer (XXI), this corresponds to molar ratios of the two blocks of (diamine-sebacic acid) (A₄-C₁ blocks) and (ED-600-sebacic acid) (B₄-C₁ blocks) between about 0.97:0.03 and about 0.57:0.43.

Example 20

Co-poly- {[N,N'-succinyl-*bis*-(L-leucine)-1,3-propylene diester]_{0.82}-[succinyl-PEG600 diester]_{0.18}} having formula (XXII) can be synthesized and used in practice of the invention. This copolymer belongs to category (C), type (A₁-B₃-C₁), described above.



(XXII)

To synthesize the copolymer (XXII), about 26.8 g (about 0.227 mole) succinic acid, and about 52.3 g (about 0.454 mole) N-hydroxysuccinimide can be added to about 100 ml dry N,N'-dimethylformamide, at room temperature, under nitrogen and dissolved with stirring. About 93.67 g (about 0.454 mole) dicyclohexylcarbodiimide (DCC) can be to the mixture added and the mixture can be allowed to stir for about 16 hours at room temperature.

The reaction mixture can be filtered through filter paper to remove the urea byproduct and the solution can be placed into a reaction flask. The following compounds can then be
10 added to the reaction mixture, with continued stirring:

(a) about 55.9 g (about 0.185 mole) the free base of *bis*-(L-leucine)-1,3-propylene diester; and

(b) about 25 g (about 0.0417 mole) poly(ethylene glycol) having molecular weight of about 600 Daltons (PEG600).

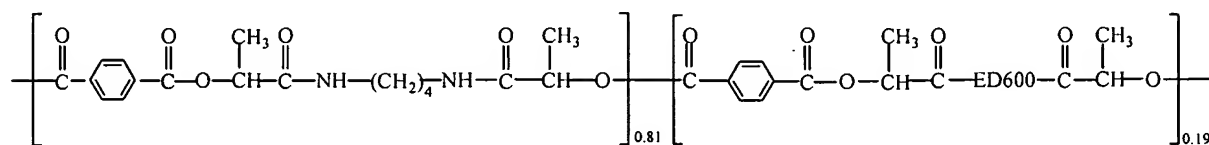
15 The mixture can be stirred at room temperature for about 2 hours and then the temperature can be increased to about 60°C and stirred for about two more hours. The polymer can be precipitated by adding the reaction solution dropwise to about 2 liters of ethyl acetate with stirring. The precipitated polymer can be placed as a thin layer into a TEFLON pan, and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

In this category, both amide and ester bonds are present in the copolymer.

Accordingly, mild conditions need be used, as understood by those having ordinary skill in the art. For example, carboxylate groups activated by carbodiimides can be used or good leaving groups such as *para*-nitro-phenol can be used. The mass contents of PEG in the final copolymer (XXII) can be between about 5 mass % and about 50 mass %. For copolymer (XXII), this corresponds to molar ratios of the two blocks of (leucine/propanediol-succinic acid) (A₁-C₁ blocks) and (PEG-diol-succinic acid) (B₃-C₁ blocks) between about 0.94:0.06 and about 0.12:0.88.

Example 21

Co-poly-{{terephthaly-*bis*-(D,L-lactate)-1,4-butylene diamide}_{0.81}-[terphthaly-*bis*-(glycolate)-ED600 diamide]_{0.19}} having formula (XXIII) can be synthesized and used in practice of the invention. This copolymer belongs to category (D), type (A₂-B₂-C₁), described above.



(XXIII)

To synthesize the copolymer (XXIII), the following compounds can be combined in a reaction flask equipped with nitrogen atmosphere, vacuum port, and heating mantle:

(a) about 0.12 g (about 3.5×10^{-4} moles) titanium tetrabutoxide;

(b) about 41.2 g (about 0.178 mole) *bis*-(D,L-lactate)-1,4-butylene diamide;

(c) about 29.83 g (about 0.0417 mole) *bis*-(glycolate)-ED600 diamide, where(ED-600 is as described above; and

(d) about 42.6 g (about 0.219 mole) dimethyl terephthalate.

The flask can be sealed and heated to about 180°C for about 2 hours. After about 2
5 hours, the pressure can be reduced to about 0.1 Torr, and the solution can be maintained at about 180°C for about two more hours.

In this category, only ester bonds present in the copolymer. Amide bonds may, or may not, be present in the reagents. Accordingly, transesterification reactions, under dehydrating conditions, in the presence of the Lewis or Bronsted acid catalysts can be used. Use of acid
10 chlorides is also a viable synthetic technique because the only hydrolysable bonds that may be present in the reagents are stable amide bonds. The mass contents of PEG in the final copolymer (XXIII) can be between about 5 mass % and about 50 mass %. For copolymer (XXIII), this corresponds to molar ratios of the two blocks of (A₂-C₁ blocks) (B₂-C₁ blocks) between about 0.97:0.03 and about 0.49:0.51.

15 Example 22

A first composition can be prepared, the composition including:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % co-poly- $\{[N,N'$ -sebacoyl-bis-(L-leucine)-1,6-hexylene diester]_{0.75}-[N,N'-sebacoyl-L-lysine benzyl ester]_{0.25}};

20 (b) between about 0.1 mass % and about 2.0 mass %, for example, about 0.5 mass% paclitaxel; and

(c) the balance, a solvent blend of ethanol and 1,1,2-trichloroethane, where the mass ratio between ethanol and 1,1,2-trichloroethane can be about 1:1.

The first composition can be applied onto the surface of bare 12 mm VISION stent (available from Guidant Corporation). Coating can be sprayed and dried to form a drug-polymer layer. A spray coater can be used having a 0.014 round nozzle maintained at ambient temperature with a feed pressure of about 2.5 psi (0.17 atm) and an atomization pressure of about 15 psi (1.02 atm). Coating can be applied at about 20 µg per pass. Between the passes the stent can be dried for about 10 seconds in a flowing air stream at about 50°C. About 270 µg of wet coating can be applied. The stent can be baked at about 50°C for about one hour, yielding a drug-polymer layer containing about 250 µg of dry coating.

A second composition can be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % copolymer (XX) described in Example 18; and

(b) the balance, a solvent blend of ethanol and 1,1,2-trichloroethane, where the mass ratio between ethanol and 1,1,2-trichloroethane can be about 1:1.

The second composition can be applied onto the dry drug-polymer layer, to form the topcoat layer. The same spraying technique and equipment can be used for the applying the topcoat layer as described for the drug-polymer layer. About 120 µg of wet coating can be applied, followed by drying, e.g., baking at about 50°C for about one hour, yielding about 100 µg of a biocompatible topcoat layer.

Example 23

A first composition can be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass%
 copolymer co-poly- $\{[N,N'$ -sebacoyl-bis-(L-leucine)-1,6-hexylene diester] $\}_{0.75}$ - $[N,N'$ -sebacoyl-
 5 L-lysine-4-amino-TEMPO amide] $\}_{0.25}$ }; and

(b) the balance, 100% ethanol

The first composition can be applied onto the surface of bare 12 mm VISION stent
 using equipment and coating technique described in Example 22. About 120 μ g of wet
 coating can be applied. The stents can be baked at about 50°C for about one hour, yielding
 10 about 100 μ g of a dry primer layer. The copolymer forming the primer layer includes 4-
 amino-TEMPO (4-amino-2,2',6,6'-tetramethylpiperidine-1-oxy) moiety attached to lysine via
 an amide linkage.

A second composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 3.0 mass %, for example, about 2.0 mass%
 15 EVEROLIMUS; and

(b) the balance, 100% ethanol.

The second composition can be applied onto the dry primer layer, to form the pure
 drug layer. The same spraying technique and equipment can be used for the applying the drug
 layer as described above. Coating can be applied at about 20 μ g per pass. Between the passes
 20 the stent can be dried for about 10 seconds in a flowing air stream at about 50°C. About 110

µg of neat drug coating can be applied. The stent can be baked at about 50°C for about one hour, yielding a pure dry drug- layer containing about 100 µg of dry coating.

A third composition can be prepared by mixing the following components:

(a) between about 0.5 mass % and about 10 mass %, for example, about 1.0 mass %

5 copolymer (XX) described in Example 18;

(b) between about 0.5 mass % and about 10 mass %, for example, about 1.0 mass %

co-poly- {[N,N'-sebacoyl-bis-(L-leucine)-1,6-hexylene diester]_{0.75}-[N,N'-sebacoyl-L-lysine benzyl ester]_{0.25}} described in Example 22; and

(c) the balance, 100% ethanol.

10 The third composition can be applied onto the dry pure drug layer, to form the topcoat layer. The same spraying technique and equipment can be used for the applying the topcoat layer as described above. About 440 µg of wet coating can be applied, followed by drying, e.g., baking at about 50°C for about one hour, yielding about 400 µg of a biocompatible topcoat layer which can also control the release of the drug.

15 While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.